RECEIVED
CENTRAL FAX CENTER

MAY 23 2005

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Serial No. 09/977,155

Applicant: Herz et al.

Filed: October 12, 2001

Docket No. UTSD:0862

Title: *LDL Receptor Signaling Assays*

Customer No. 23379

Confirmation No. 3854

Group Art Unit: 1641

Examiner: Cook, L.

CERTIFICATE OF TRANSMISSION
I hereby certify that this corr is being transmitted by facsimile to the Comm for Patents 703-872-9306 on May 23, 2005.

Signature _____
Richard Aron Osman

RESPONSE

The Commissioner for Patents
Washington, DC 20231

Dear Examiner Cook:

Thank you for the Action May 18, 2005.

35USC102(b)

Willnow et al. (1994, J Biol Chem 269, 15827-32) describe the production and functional analysis of truncated LRPs comprising subsets of the of the native N-terminal, extracellular domains (Fig. 1). One minireceptor was partially cleaved at a known region IV proteolytic processing site (Fig. 2A, lanes 2 and 4). LRP is known to be naturally proteolyzed at this extracellular N-terminal proteolytic processing site to generate two subunits: a 85 kd membrane spanning beta subunit, and a larger 515 kd N-terminal alpha-subunit which lacks a membrane-spanning region, but remains attached to the membrane through noncovalent association with the smaller C-terminal beta-subunit (Herz et al. (1990, EMBO J 9, 1769-1776).

The present inventors disclose that LRP and other members of the LDL receptor gene family undergo distinct endoproteolytic processing events *that result in the release of their cytoplasmic tails into the cytoplasm*. Specification, p.1, liens 24-26. To release a cytoplasmic tail, the disclosed processing need to occur at intramembranous or cytoplasmic sites – not the N-terminal, extracellular region IV processing site known in the art, which liberates an extracellular domain, and not a cytoplasmic tail.

Accordingly, all our claimed methods are for detecting proteolysis of an LDL receptor transmembrane domain, and require a cell membrane comprising (i) a polypeptide comprising an LDL receptor transmembrane domain fused to a C-terminal tail, and (ii) a protease which

specifically cleaves the domain and thereby releases the tail from the membrane. In contrast, Willnow describes an LRP which is cleaved at an N-terminal, extracellular site, and the protease does not and cannot release from the membrane any C-terminal tail.

The Examiner correctly observes that Willnow et al. describe using an anti-LRP antibody directed against the cytoplasmic tail of LRP to identify unprocessed precursor (region IV) and the processed 85-kDa carboxyl-terminal fragment (Fig 2; para. bridging p.15828-15829) on immunoblots made from extracted and partially purified membrane proteins. Accordingly, in Willnow the carboxyl-terminal fragment is released from the membrane not by the protease, but rather by subsequent biochemical extraction. In Willnow, protease cleavage at the N-terminal, extracellular region IV processing site yields a membrane-bound fragment. The membrane-bound C-terminal cleavage produce is then biochemically extracted from the membrane. In contrast, our claims require that cleavage by the protease release the tail from the membrane, which does not and cannot occur in Willnow's work.

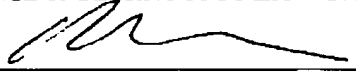
35USC103(a)

Willnow has been described above. Herz (2001, Neuron 29, 571-81) describes LDL receptor family proteins, and reviews the diverse physiological roles that these receptors have been found to play. However, nowhere does Herz disclose or suggest producing and detecting a protease liberated C-terminal tail of any LDR receptor as required by our claims.

The Examiner is invited to call the undersigned if he would like to amend the claims to clarify the foregoing or seeks further clarification of the claim language.

We petition for and authorize charging our Deposit Account No.19-0750 all necessary extensions of time. The Commissioner is authorized to charge any fees or credit any overcharges relating to this communication to our Dep. Acct. No.19-0750 (order UTSD:0862).

Respectfully submitted,
SCIENCE & TECHNOLOGY LAW GROUP



Richard Aron Osman, J.D., Ph.D., Reg. No. 36,627
Tel (949) 218-1757; Fax (949) 218-1767

"To Help Our Customers Get Patents"
Mission Statement, USPTO External Customer Services Guide

PAGE 2/2 * RCVD AT 5/23/2005 2:02:52 PM [Eastern Daylight Time] * SVR:USPTO-EFXRF-1/3 * DNIS:8729306 * CSID:1 949 218 1767 * DURATION (mm-ss):01-00